

When to suggest this OC alternative *J Fam Pract.* 2009;58(4):207-210.

Potential PURL Review Form: Randomized controlled trials

SECTION 1: IDENTIFYING INFORMATION FOR NOMINATED POTENTIAL PURL

1. Citation Sulak PJ, Smith V, Coffee A, Witt I, Kuehl AL, Kuehl TJ. Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: a randomized controlled trial. *Obstet Gynecol.* 2008;112(3):563-571.
2. Hypertext link to PDF of full article <http://journals.lww.com/greenjournal/pages/articleviewer.aspx?year=2008&issue=09000&article=00010&type=abstract>
3. First date published study available to readers September 2008
4. PubMed ID 18757653
5. Nominated By Sarah-Anne Schumann
6. Institutional Affiliation of Nominator University of Chicago
7. Date Nominated September 2, 2008
8. Identified Through Other: OB/GYN
9. PURLS Editor Reviewing Nominated Potential PURL Bernard Ewigman
10. Nomination Decision Date September 3, 2008
11. Potential PURL Review Form (PPRF) Type RCT
12. Other comments, materials or discussion
13. Assigned Potential PURL Reviewer Debra Stulberg
14. Reviewer Affiliation University of Chicago

15. Date Review Due October 2, 2008

Due

16. Abstract OBJECTIVE: To assess bleeding patterns with continuous use of the transvaginal contraceptive ring. METHODS: We did a prospective analysis of daily menstrual flow during a 21/7 cycle followed by 6 months of continuous use and institution of a randomized protocol to manage breakthrough bleeding/spotting. Seventy-four women completed the baseline 21/7 phase and were randomized equally into 2 groups during the continuous phase. Group 1 was instructed to replace the ring monthly on the same calendar day with no ring-free days. Group 2 was instructed to use the same process, but if breakthrough bleeding/spotting occurred for 5 days or more, they were to remove the ring for 4 days, store it, and then reinsert that ring. RESULTS: Sixty-five women completed the continuous phase with reduced average flow scores in the continuous phase compared with the 21/7 phase ($P<.02$). Most patients had no to minimal bleeding during continuous use, with group 2 experiencing a statistically greater percentage of days without breakthrough bleeding or spotting (95%) compared with group 1 (89%) ($P=.016$). Instituting a 4-day hormone-free interval was more ($P<.001$) effective in resolving breakthrough bleeding/spotting than continuing ring use. CONCLUSION: A reduction in bleeding occurred during continuous use with replacement of the transvaginal ring compared with baseline 21/7 use. Continuous vaginal ring use resulted in an acceptable bleeding profile in most patients, reduction in flow, reduction in pelvic pain, and a high continuation rate.

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. Number of patients starting each arm of the study? 38 in group 1 (continuous use of vaginal ring), 37 in group 2 (continuous use of vaginal ring with 4-day hormone-free interval allowed if patient experiences 5 consecutive days of spotting)
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?
Inclusion: Women age 18-45 who had been using combined hormonal contraceptives (pill, patch, or ring) on a 21-days-on/7-days-off cycle for 2 or more months.
Exclusion: BMI 38 or higher; contraindications to combined hormonal contraception; tobacco use >10 cigarettes per day; taking antiretroviral agents; using other estrogen or phytoestrogen products; desire for pregnancy within 1 year; pelvic ultrasound findings of endometrial thickness >8 mm or ovarian cyst >2.5 cm.
3. Intervention(s) being investigated? Continuous use of NuvaRing (replace ring monthly with no hormone-free interval) and continuous use with allowed 4-day hormone-free interval
4. Comparison treatment(s), placebo, or nothing? Subjects completed 1-2 months of 21/7 NuvaRing regimen (FDA-approved dosing) and then 6 months of a continuous dosing regimen, in which the ring is left in for a month and changed on the same calendar day of each month. Two comparisons were examined: (1) Traditional 21/7 regimen versus continuous dosing. This comparison was not done by randomization, rather by prospective observation of all participants. (2) During the continuous-use phase of the study, participants were randomized to continuous without a break (group 1) versus continuous with 4-day hormone-free interval allowed for spotting.
5. Length of follow-up? Note specified end points e.g. death, cure, etc. 6 months.
6. What outcome measures are used? List all that assess effectiveness. Participants completed a Scott and White Daily Diary of Symptoms, which scores occurrence and degree of menstrual flow, pelvic pain, headaches, and mood: (1) Menstrual flow scored 0 (no spotting or bleeding) to 4 (heavy flow, soaking 6 or more tampons/pads in a day); (2) pelvic pain VAS 0-10; (3) headache VAS 0-10; and (4) mood symptoms (depression, anxiety, irritability) VAS 0-10.

7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, *P*-values, etc.

The main results (Table 2) were provided only for subjects who completed all 6 months of data collection (n=29 in group 1, n=36 in group 2). During the continuous (randomized comparison) phase of the study, group 2 (allowed a 4-day hormone-free interval) had a statistically greater percentage of days without bleeding or spotting (95%) compared with group 1 (no hormone-free interval) (89%), *P*=.016, NNT=8.3. But average daily flow was no different across groups (average flow score = 0.21 in group 1 vs 0.17 in group 2, *P*=.38). In both groups, average daily flow was significantly lower during the continuous-use phase than the 21/7 phase (nonrandomized comparison) (group 1 average score = 0.33 during 21/7 vs 0.21 during continuous phase, *P*=.012; group 2 average score = 0.38 during 21/7 vs 0.17 during continuous phase, *P*<.001). Percent of flow-free days was significantly lower in the continuous phase for group 2 compared with during the 21/7 phase for this group (95% vs 83%, *P*<.001). This improvement did not reach statistical significance for group 1 (89% flow-free days during continuous use vs 85% during 21/7 phase, *P*=.086).

Figure 4 reports an intent-to-treat analysis of 108 episodes of spotting or bleeding >5 consecutive days (taken from both groups) comparing patients assigned to hormone-free interval (ring removal) with patients assigned not to remove the ring. A statistically significant difference was noted in bleeding patterns (*P*<.001), with the removal group experiencing higher flow scores on days 1, 2, and 3 of the hormone-free interval and lower scores beginning 8 days after the start of the interval. The text and figure on this analysis are confusing regarding intent-to-treat. For example, the text states that there was some cross-over (patients assigned NOT to have a hormone-free interval took one anyway, and patients allowed one decided not to take it), and it states that the analysis is intent-to-treat, but then it states, "removal of the ring resulted in..." which sounds like an as-treated finding rather than intent-to-treat.

Finally, headaches, mood symptoms, and pelvic pain did not differ between groups 1 and 2 during the continuous (randomized comparison) phase of the study. Comparing the 21/7 phase to the continuous phase, pelvic pain was significantly better during continuous use (0.32 vs 0.18, *P*=.001, scale is 0-10). Headaches and mood symptoms were not statistically significantly better, although headache favored the continuous phase (0.45 vs 0.32, *P*=.066).

8. Study addresses an appropriate and clearly focused question - **select one**

- Well covered
- Adequately addressed
- Poorly addressed
- Not applicable

9. Random allocation to comparison groups - **select one**

Well covered

10. Concealed allocation to comparison groups - **select one**

Well covered

11. Subjects and investigators kept "blind" to comparison group allocation - **select one**

Well covered

Comments: Subjects could not be blinded because the intervention was to offer them the option of removing the ring when bleeding symptoms develop.

12. Comparison groups are similar at the start of the trial - **select one**

Well covered

- 13.** Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias. - ***select one*** Well covered
- 14.** Were all relevant outcomes measured in a standardized, valid, and reliable way? - ***select one*** Adequately addressed
- 15.** Are patient-oriented outcomes included? If yes, what are they? Yes, all outcomes are patient-oriented: They are symptoms of vaginal bleeding or spotting, headaches, pelvic pain, or mood problems.
- 16.** What percent dropped out, and were lost to follow up? Could this bias the results? How? Of the 75 participants meeting inclusion criteria and completing the baseline (21/7 dosing) phase, 1 person dropped out of group 1 during the continuous phase due to a side effect the authors weren't studying (vaginal discharge) and they removed this person from analysis altogether. Of the sample the authors then counted (n=74), 8 subjects (22%) dropped out from group 1: 4 due to relevant side effects (mood lability, headache, or bleeding), 2 who couldn't attend scheduled visits, 1 who desired pregnancy, and 1 who was lost to follow-up. From group 2, only 1 subject (3%) dropped out, due to desiring pregnancy. These drop-out rates are statistically significantly different. Drop-outs are not included in the main analysis (Table 2) because their data are incomplete or missing. Although drop-outs would seem to bias the results toward the observed effect, (ie, if the vaginal ring is kept in, the effect favoring group 2 would probably have been stronger because group 1 had more symptom-related drop-outs), I still would have liked to see a sensitivity analysis, which the authors did not provide: eg, "If we assumed all drop-outs had the highest symptom score given among continuing participants, it would have affected our results as follows...."
- 17.** Was there an intention-to-treat analysis? If not, could this bias the results? How? It's not totally clear. For the main results (Table 2), no mention is made of cross-overs, so I assume they analyzed as-randomized (although they don't explicitly say so). For the figure 4 results, they specifically refer to it as an intention-to-treat analysis but then use language that suggests it's actually as-treated.
- 18.** If a multi-site study, are results comparable for all sites? N/A
- 19.** Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity? Organon, the maker of NuvaRing, provided support in the form of an unrestricted educational grant, and the authors received salary support from Organon. However, because this study is a comparison of different NuvaRing regimens (rather than NuvaRing vs placebo or another agent), I'm not as worried about this bias. It is possible that studies showing horrible side effect profiles might have been suppressed by the funding organization.

- 20.** To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized. Any patient who qualifies for the NuvaRing as a contraceptive method.
- 21.** In what care settings might the findings apply, or not apply? Any
- 22.** To which clinicians or policy makers might the findings be relevant? Primary care and Ob/Gyn providers.

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date Forman PD, Baines H (reviewers). Contraceptive patch and vaginal rings. In: DynaMed [database online] Available at <http://www.dynamicmedical.com/> Last updated March 10, 2009. Accessed March 12, 2009.

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences) Based on one 1-year-long RCT, extended cycles of the contraceptive ring may reduce total bleeding days.

4. UpToDate excerpts

5. UpToDate citation/access date Management of unscheduled bleeding in women using contraception.

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Last literature review version 16.2: May 2008. This topic last updated: March 31, 2008. Accessed September 29, 2008

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Continuous use of oral contraceptive pills may reduce total bleeding days, and if unscheduled bleeding becomes a problem, a short hormone-free interval can be advised for patients using pills continuously. There are no studies on ways to reduce unscheduled bleeding with the contraceptive ring.

7. PEPID PCP excerpts

If ring left in place >3 weeks: remove for 1 week; rule out pregnancy, then insert new ring; use additional form of contraception for 7 days.

8. PEPID citation/access data

NuvaRing
Background
Accessed September 29, 2008

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
 Yes, there is important evidence or recommendations that are missing
 No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
 Yes, there is important evidence or recommendations that are missing
 No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry (HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts (USPSTF; other guidelines; etc.)

Several other sources on the Internet, eg, found by Google search, describe that continuous use of NuvaRing is an acceptable alternative to the 21/7 regimen. I did not find any, though, that describe the 4-day hormone-free interval for NuvaRing.

One example, from a site sponsored by the Feminist Women's Health Center:

It is possible to use birth control pills and the NuvaRing in a continuous fashion. Most packages of birth control pills contain 3 weeks of hormone pills and 1 week of sugar pills, or spacer pills. By only taking the hormone pills and not taking the 1 week break there will be no withdrawal bleeding. This has been done for years for a variety of reasons.

Continuous hormonal birth control can help relieve symptoms of PMS, menstrual migraines, and anemia.

Athletes and women planning their wedding or vacation have been using this method to "skip their periods" for many years.

A lot of women like the idea of not having to bother with the inconvenience of a period, but the most compelling reason to choose continuous hormonal use is to decrease the risk of unwanted pregnancy.

Use birth control pills: Only monophasic birth control pills can be used. Monophasic pills contain the same amount of hormones in each pill. Take a hormonal pill every day. Do not take the spacer pills.

NuvaRing: Insert one NuvaRing every 3 weeks without skipping any days. Never go without a ring inserted.

11. Citations for <http://www.birth-control-comparison.info/continual-hormones.htm>. Accessed September 29, 2008.
other excerpts

SECTION 4: CONCLUSIONS

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) 3

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) 2

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) 2

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

The potential new practice recommendation is to offer women the NuvaRing in a continuous rather than 21-days-on-7-days-off dosing regimen (which is not totally new) and, among women using the ring continuously, to offer them a 4-day interval of removing the ring in the middle of the month if symptoms of spotting/bleeding occur for 5 consecutive days.

7. Applicability to a Family Medical Care Setting:

1

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.

9. Immediacy of

2

Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7

(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

The biggest (probably only) barrier to implementation is the complexity of the regimen and possible difficulty of explaining it to patients during counseling. I already have a difficult time offering patients the continuous regimen and explaining what I mean, because the package insert says 21 days in, 7 days out. To add the "continuous, but if you experience 5 days of spotting in the middle of the month, you can remove the ring for 4 days, then put it back in, but then change again on the day you otherwise would have" may be too complicated for some patients (or practitioners). But for those who are motivated, it's probably not too hard.

3

11. Clinical meaningful outcomes or patient-oriented outcomes:

Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

They are patient-oriented. Whether the effect size is large enough to be clinically meaningful (95% of days without bleeding vs 89%) is debatable.

5

13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)

Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family

physicians do in medical care settings and seems different than current practice.

- Applicability in medical setting:
- Immediacy of implementation

14. Comments on your response in 4.13

I like this option: continuous use of the ring, with optional 4-day hormone-free interval. For some patients, I can see recommending it. And it does appear to be novel. On the other hand, this study is small, there were a good number of drop-outs with no data and no sensitivity analysis, the results are poorly described (eg, was it intention to treat or not?), and the effect size, where positive, is small.

SECTION 5: EDITORIAL DECISIONS

1. FPIN PURLs editorial decision (select one)

Pending PURL

2. Follow-up issues for Pending PURL Reviewer

Polls

3. FPIN PURLS Editor making decision

Bernard Ewigman

4. Date of decision

October 2, 2008